has been indicated and a proper assessment of these rejections can be made. A rejection of claim 5 for indefiniteness also is pending, which should be moot once the present claims have been entered.

The Examiner's Action rejected claims 1-6, 8 and 9 as obvious over *Huxley et al.* taken with *Hooper et al.* and *Pachnis et al.* Claims 7, 10 and 11 were rejected as obvious over *Hooper* taken with *Huxley* and *Pachnis et al.* Respectfully, the Examiner's Action relies upon a mere speculation (not evidence) that spheroplast fusion techniques could be transferred from L cells to ES cells, while the record contains direct evidence from subsequent journal articles that techniques such as spheroplast fusion that work in L cells were "highly inefficient and irreproducible" in ES cells. Thus, the evidence of record does not support a conclusion that the claims would have been obvious.

The burden of establishing a case of *prima facie* obviousness rests with the Patent and Trademark Office. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Moreover, an obviousness rejection "must be based on *evidence* (statutory prior art, admissions against interest)... ." *In re McKellin*, 188 USPQ 428, 432 (CCPA 1976), emphasis in original. In this case, Applicants introduced persuasive evidence of nonobviousness into the record via their previous amendment; however, that evidence has not fairly been considered.

The hindsight assembling of selected portions of prior art references cited against Applicants' claims, as the Examiner's Action has done here, is legally improper according to the case law, such as *Orthopedic Equipment Company v. U.S.*, 217 USPQ 193, 199 (Fed. Cir. 1983). Thus, once references have been chosen by an examiner:

> It is impermissible within the framework of § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Wesslau, 147 USPQ 391, 393 (CCPA 1965). In an obviousness analysis, "prior art references ... must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention." See, for example, Akzo NV v. International Trade Commission, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986). As explained below, the cited references considered as a whole, and taken with those articles submitted for the record by Applicants, do not suggest the claimed invention.

The abstract of the *Pachnis et al.* paper expresses its authors' intention "to test the feasibility of transferring yeast artificial chromosomes (YACs) into mammalian cells." This "feasibility test" was further described on page 5109, left col., where the authors reported that a YAC carrying human DNA and a neomycin-resistance gene can be transferred efficiently from *S. cerevisiae* cells into mouse fibroblasts (L cells not ES cells) in culture by cell fusion. *Pachnis et al.*, did not "test for expression of any human genes transferred on the YAC", although the neomycin resistance gene, which utilized a mammalian promoter and enhancer, was expressed. (See page 5113, left col.) The authors speculated that:

> "The application of this YAC transfer system to pluripotent embryonic stem cells [referring to two (2) 1981 publications], which are capable of colonizing the somatic as well as the germ cell lineages when implanted into early mouse embryos [citing a

> 1984 paper], could lead to the generation of transgenic animals that carry and transmit any YAC.

(page 5113, left col., last paragraph.)

In response to Applicants' previous arguments that the excerpted statement provides no reasonable expectation of success, the Examiner's Action responded by finding an inference of a reasonable expectation of success under a theory that *Pachnis et al.* would not have suggested substituting ES cells for L cells if the substitution would not work. Respectfully, the Examiner's Action draws an unreasonable and unwarranted conclusion from the excerpted statement in the reference, based on the entire record of this case. The reference does not say that L and ES cells were equivalent, and it provides no extra guidance for transforming ES cells. The phase "could lead to" if, for example found in an Applicant's specification in most any application, would immediately be rejected by an Examiner under § 112, first paragraph, as entirely speculative and providing no reasonable expectation that such a step could be practiced without undue experimentation. Conversely, this statement in a reference that does not even attempt to create germ-line transformed transgenic animals does not convey a reasonable expectation of success that such animals could be made.

Also part of the record is the *Strauss et al.* (1993) paper, submitted by Applicants with their previous Amendment, which explained that transfection of ES cells with protocols useful in introducing YAC DNA into fibroblasts "proved to be highly inefficient and irreproducible." (Page 1905, left col., second full paragraph.) Thus, the record contains evidence that techniques useful in transfecting fibroblasts would not have been

expected to work in ES cells as has now been disclosed and claimed by Applicants. Notably, the *Pachnis et al.* paper, relied upon heavily by the Examiner's Action, was communicated to PNAS on 16 April 1990, yet much later as of 23 November 1992 when *Strauss et al.* (1993) was submitted to Science, the latter paper reported that "Other methods of introducing YAC-sized DNA into mammalian cells have been used, including spheroplast fusion and microinjection [citing to references including that of *Pachnis et al.*], but no successful transfection of ES cells have been reported to date. (Page 1907, left col., last paragraph.) Thus, the *Pachnis et al.* techniques were not readily applied to ES cells, notwithstanding the great interest in the field of transforming germ line cells.

Applicants also submitted a second article by *Strauss et al.* (1992) with the previous Amendment. This paper described the introduction of the entire yeast genome into L cells by spheroplast fusion and other techniques [again citing to several papers including that of *Pachnis et al.*], (p. 417, right col., first full paragraph). However, this paper reported that the presence of large portions of yeast genome present as contaminants "could be mutagenic, and thus deleterious to the capacity of a ES cell to contribute to the germ line of a chimeric mouse." (Page 421, right col., third full paragraph.) Rather than follow the techniques of the prior art, e.g., spheroplast fusion, *Strauss et al.* (1992) employed an alternative approach (lipid micelles) that was "directed at developing a transfection protocol utilizing highly purified YAC DNA," introduced into mutant fibroblasts via DNA-lipid micelles. Employing that protocol, rather than spheroplast fusion, the authors reported that they were "testing ES cells, containing

intact YAC DNA for their contribution to the germline." (page 421, right col.) Note, however, that *Strauss et al.* (1993) subsequently concluded that transfection of ES cells with DNA-lipid micelles was "highly inefficient and irreproducible." (Page 1905, left col., second full paragraph.) Several modifications were necessary to be incorporated into that transfection protocol.

Taken for what they fairly disclose to one skilled in the art, the two *Strauss et al.* papers report that the specific *Pachnis et al.* fibroblast fusion technique was problematic. Moreover, even another protocol useful in transferring YAC DNA to L cells (i.e., lipid micelles) was found to be highly inefficient and irreproducible when applied to ES cells. Taken for what they fairly suggest to one skilled in the art, this evidence of record hardly would leave the skilled artisan with a reasonable expectation that spheroplast fusion of embryonic stem cells using the *Pachnis et al.* protocol would have been successful.

The Federal Circuit Court of Appeals has repeatedly articulated the requirements of a proper obviousness analysis:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, ... 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and

> the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure.

In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced because the cited art and other evidence of record does not fairly suggest that the methods claimed be carried out with a reasonable expectation of success.

The Examiner's Action considers that the *Strauss et al.* papers do not teach away from using the spheroplast fusion technique for ES cells and further considers that the problems in utilizing the protocols of *Pachnis et al.* would have been overcome simply by preparing and screening more clones. (See Examiner's Action at page 5.) Respectfully, the record does not support such a conclusion. *Strauss et al.* (1992) explained that large portions of the genome as "contaminating material could be mutagenic, and thus deleterious to the capacity of an ES-cell to contribute to the germ line of a chimeric mouse. It was for <u>this</u> reason that our efforts were directed at developing a transfection protocol utilizing higher purified YAC DNA" (page 421, right col., second full paragraph, emphasis added.) In other words, *Straus et al.* was concerned about mutagenesis -- not simply the logistics of screening more cells. Thus, the evidence of record explains that *Strauss et al.* utilized lipid micelles as an alternative technique to spheroplast fusion, thereby teaching away from the *Pachnis et al.* procedures, not because of an inability to screen larger numbers of clones, but rather to avoid the mutagenic impact of the presence of a large amount of yeast DNA.

With respect to an additional paper submitted with Applicants' previous amendment by *Pavan et al.*, both Applicants and the Examiner cite to the same portion of the paper in support of their positions. Respectfully, *Pavan et al.* states that, while it would be desirable to transfer DNA segments from YAC into the mammalian germ line via ES cells, the "successful use of this procedure to generate transgenic mice would require the development of PEG fusion techniques in which ES cells retain the ability to colonize the germ line of the chimera, an ability which is readily lost during the manipulations of these cells." The Examiner's Action interprets this statement as explaining that the ability to colonize a germ line is lost during the manipulation of ES cells independent of whether or not PEG is present. However, taking the Examiner's understanding as correct, one skilled in the art would learn from *Pavan et al.* that ES cells are fragile and loose the ability to colonize germ lines. This would not increase whatever expectations of success remained after a consideration of the other evidence of record previously discussed.

Similarly, the *Bradley et al.* paper, also submitted by Applicants with their previous amendment, discusses "Future Directions", and states that "it still remains technically very difficult to effect such a transfer [i.e., the potential transfer of large genes using YAC vectors] and it is unknown whether ES cells modified with YACs will be able to repopulate the germline of mice." (Page 537.) Based on what this additional evidence of record fairly discloses, there is no factual basis for concluding that one skilled in the art would have had a reasonable expectation of success in practicing the invention claimed by the present Applicants.

With respect to the rejection of claim 12 for obviousness, the additional references *Traver et al.*, *Sumizo et al.*, and *Burman et al.* do not fill the gaps left by the primary and secondary references discussed above. Thus, notwithstanding knowledge of transgenes containing rearranged human immunoglobulin-related genes, one skilled in the art still would have had no reasonable expectation of success in the methods disclosed in claim 12 as set forth by Applicants. Accordingly, no *prima facie* case of obviousness has been set forth for claim 12.

To the extent that the Examiner's Action considers Applicants' claims to have been obvious to try, this is not applicable legal test. As explained in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USQP2d 1016, 1021 (Fed. Cir. 1991), in which patentability of the gene to erythropoietin (EPO) was at issue:

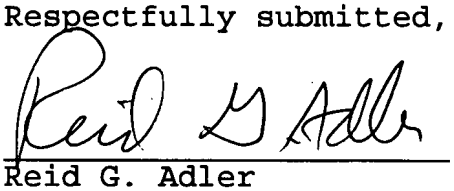
> ...none of the prior art references 'suggest[s]' that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest .... While [the trial court] found that defendants had shown that these procedures were 'obvious to try,' the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022.

Similarly, here, the record does not fairly teach or suggest that the success of Applicants' invention would reasonably have been expected.

C O N C L U S I O N S

For the reasons set forth above, withdrawal of the finality of rejection for the previous Examiner's Action would be appropriate. Moreover, the record does not support a conclusion that one skilled in the art would have had a reasonable expectation of success in practicing the invention claimed by Applicants. For these reasons, entry of the claims and their passage to allowance is respectfully requested.

Respectfully submitted,

By: 
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